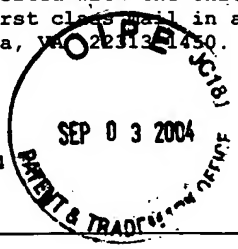
CERTIFICATE OF MAILING (37 CFR 1.8a)

IFW

I hereby certify that this paper (along with any paper referred to as being transmitted therewith) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



Kimberly J. Prior
(Print Name)

(Signature)

Date: September 1, 2004

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1632

Synese Jolidon, et al.

Serial No.: 10/666,594

Filed: September 18, 2003

For: **4-PYRROLIDINO-PHENYL-BENZYL ETHER DERIVATIVES**

TRANSMITTAL OF CERTIFIED COPY

September 1, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	02021319.5	September 20, 2002

Respectfully submitted,

Kimberly J. Prior
Attorney for Applicant
Reg. No. 41483
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
Phone: (973) 235-6208

KJP/bah
Enclosures

Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02021319.5

CERTIFIED COPY OF PRIORITY DOCUMENT

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02021319.5
Demande no:

Anmeldetag:
Date of filing: 20.09.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

F. HOFFMANN-LA ROCHE AG

4070 Basel
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

4-Pyrrolidino-phenyl-benzyl ether derivatives as MAO-B inhibitors

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D207/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

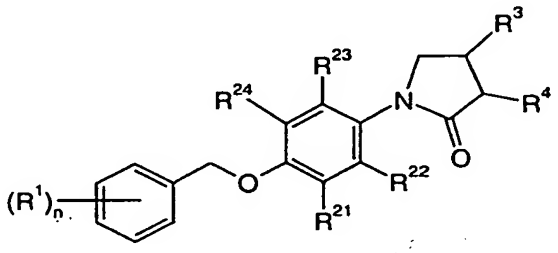
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

Case 21326

4-Pyrrolidino-phenyl-benzyl ether derivatives as MAO-B inhibitors

This invention relates to racemic or enantiomerically pure 4-pyrrolidino-phenyl-benzyl ether derivatives of the general formula



I

wherein

R^1 is halogen, halogen-(C_1-C_6)-alkyl, cyano, C_1-C_6-alkoxy or halogen-(C_1-C_6)-alkoxy;

R^{21}, R^{22}, R^{23} and R^{24} independently from each other are selected from the group consisting of hydrogen and halogen;

either

R^3 is $-CONHR^5$, $-CH_2CN$, -CN or $-NHR^6$, and R^4 is hydrogen;

or

R^3 is hydrogen, and R^4 is $-CONHR^5$, $-CH_2CN$, -CN or $-NHR^6$;

R^5 is hydrogen or C_1-C_3-alkyl;

R^6 is $-CO$-(C_1-C_6)-alkyl or $-SO_2$-(C_1-C_6)-alkyl; and

n is 0, 1, 2 or 3;

as well as individual isomers, racemic or non-racemic mixtures thereof.

DK / 18.09.2002

It has been found that the compounds of general formula I are selective monoamine oxidase B inhibitors.

Monoamine oxidase (MAO, EC 1.4.3.4) is a flavin-containing enzyme responsible for the oxidative deamination of endogenous monoamine neurotransmitters such as dopamine, serotonin, adrenaline, or noradrenaline, and trace amines, e.g. phenylethylamine, as well as a number of amine xenobiotics. The enzyme exists in two forms, MAO-A and MAO-B, encoded by different genes (A. W. Bach et al., *Proc. Natl. Acad. Sci. USA* 1988, *85*, 4934-4938) and differing in tissue distribution, structure and substrate specificity. MAO-A has higher affinity for serotonin, octopamine, adrenaline, and noradrenaline; whereas the natural substrates for MAO-B are phenylethylamine and tyramine. Dopamine is thought to be oxidised by both isoforms. MAO-B is widely distributed in several organs including brain (A.M. Cesura and A. Pletscher, Prog. Drug Research 1992, *38*, 171-297). Brain MAO-B activity appears to increase with age. This increase has been attributed to the gliosis associated with aging (C.J. Fowler et al., *J. Neural. Transm.* 1980, *49*, 1-20). Additionally, MAO-B activity is significantly higher in the brains of patients with Alzheimer's disease (P. Dostert et al., *Biochem. Pharmacol.* 1989, *38*, 555-561) and it has been found to be highly expressed in astrocytes around senile plaques (Saura et al., *Neuroscience* 1994, 70, 755-774). In this context, since oxidative deamination of primary monoamines by MAO produces NH_3, aldehydes and H_2O_2, agents with established or potential toxicity, it is suggested that there is a rationale for the use of selective MAO-B inhibitors for the treatment of dementia and Parkinson's disease. Inhibition of MAO-B causes a reduction in the enzymatic inactivation of dopamine and thus prolongation of the availability of the neurotransmitter in dopaminergic neurons. The degeneration processes associated with age and Alzheimer's and Parkinson's diseases may also be attributed to oxidative stress due to increased MAO activity and consequent increased formation of H_2O_2 by MAO-B. Therefore, MAO-B inhibitors may act by both reducing the formation of oxygen radicals and elevating the levels of monoamines in the brain.

Given the implication of MAO-B in the neurological disorders mentioned above, there is considerable interest to obtain potent and selective inhibitors that would permit control over this enzymatic activity. The pharmacology of some known MAO-B inhibitors is for example discussed by D. Bentué-Ferrer et al. in *CNS Drugs* 1996, *6*, 217-236. Whereas a major limitation of irreversible and non-selective MAO inhibitor activity is the need to observe dietary precautions due to the risk of inducing a hypertensive crisis when dietary tyramine is ingested, as well as the potential for interactions with other medications (D. M. Gardner et al., *J. Clin. Psychiatry* 1996, *57*, 99-104), these adverse events are of less concern with reversible and selective MAO inhibitors, in particular of MAO-B. Thus, there

is a need for MAO-B inhibitors with a high selectivity and without the adverse side-effects typical of irreversible MAO inhibitors with low selectivity for the enzyme.

Object of the present invention therefore is to provide compounds which must have the criteria mentioned above. It has been found that the compounds of formula I of the present invention show the potential to be highly selective MAO-B inhibitors. Subjects of the present invention are further a process for the manufacture of compounds of formula I as well as the use of the compounds of formula I in the control or prevention of diseases mediated by monoamine oxidase B inhibitors, and, respectively, their use for the production of corresponding medicaments.

The following definitions of general terms used in the present patent application apply irrespective of whether the terms in question appear alone or in combination. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural forms unless the context clearly dictates otherwise.

The term "C_1-C_6-alkyl" ("lower alkyl") used in the present application denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 3 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, and the like. Accordingly, the term "C_1-C_3-alkyl" means a straight-chain or branched saturated hydrocarbon residue with 1 to 3 carbon atoms.

The term "halogen" denotes fluorine, chlorine, bromine and iodine.

"Halogen-(C_1-C_6)-alkyl" or "halogen-(C_1-C_6)-alkoxy" means the lower alkyl residue or lower alkoxy residue, respectively, as defined herein substituted in any position with one or more halogen atoms as defined herein. Examples of halogenalkyl residues include, but are not limited to, 1,2-difluoropropyl, 1,2-dichloropropyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, and 1,1,1-trifluoropropyl, and the like. "Halogenalkoxy" includes trifluoromethyloxy.

"C_1-C_6-Alkoxy" means the residue -O-R, wherein R is a lower alkyl residue as defined herein. Examples of alkoxy radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

"Pharmaceutically acceptable salts" of a compound means salts that are pharmaceutically acceptable, which are generally safe, non-toxic, and neither biologically nor otherwise undesirable, and that possess the desired pharmacological activity of the parent compound. These salts are derived from an inorganic or organic acid or base. If possible, compounds of formula I may be converted into pharmaceutically salts. It should be understood that pharmaceutically acceptable salts are included in the present invention.

Among compounds of the present invention certain compounds of formula I are preferred.

Preferred compounds of formula I are those wherein R^3 is selected from the group consisting of -CO-NHR^5, -CH_2CN, or -CN, and R^4 is hydrogen. R^5 is hydrogen or C_1-C_3-alkyl.

Especially preferred are compounds of formula I, wherein R^3 is -CO-NHR^5, R^5 is hydrogen or C_1-C_3-alkyl, and R^4 is hydrogen. A preferred group of compounds within this group of compounds of formula I are those, wherein R^5 is hydrogen.

(RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid amide is an example of such a compound.

A more preferred group of compounds of formula I are those wherein R^3 is -CO-NHR^5 and R^5 is methyl.

Examples of such compounds are the following:
(RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-[1-[4-(3,4-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-[1-[4-(2,6-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-[4-(3-chloro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-[3-fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-[2-fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
and
(R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide.

A further preferred group of compounds of formula I are those, wherein R^3 is -CH_2CN and R^4 is hydrogen. (RS)-1-[4-(3,4-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetonitrile is an example for such a compound.

Also preferred are compounds of formula I, wherein R^3 is hydrogen, and R^4 is selected from the group consisting of -CONHR^5, -CH_2CN, or -CN.

Those compounds of formula, wherein R^4 is –$CONHR^5$ and R^5 is hydrogen or C_1-C_3-alkyl, are especially preferred.

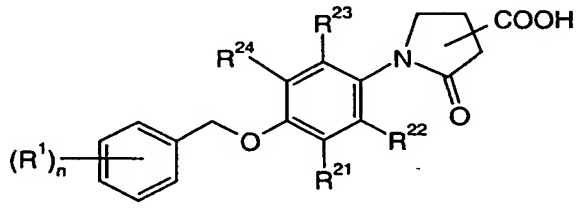
Another group of preferred compounds of formula I are those, wherein R^4 is -CN. (RS)-1-(4-benzyloxy-phenyl)-2-oxo-pyrrolidine-3-carbonitrile is an example of such a compound.

Further preferred are compounds of formula I, wherein R^3 is $-NHR^6$, R^6 is -CO-(C_1-C_6)-alkyl or $-SO_2$-(C_1-C_6)-alkyl, and R^4 is hydrogen. An example for such a compound is (RS)-N-{1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetamide.

Also preferred are compounds of formula I, wherein R^3 is hydrogen, R^4 is $-NHR^6$ and R^6 is -CO-(C_1-C_6)-alkyl or $-SO_2$-(C_1-C_6)-alkyl.

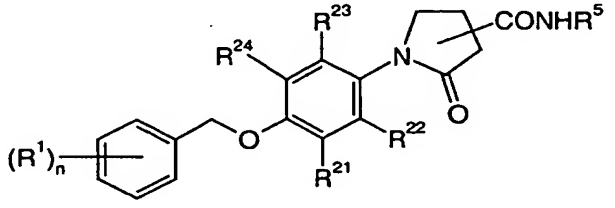
Compounds of formula I may be substituted by n R^1 selected from the group consisting of halogen, halogen-(C_1-C_6)-alkyl, cyano, C_1-C_6-alkoxy or halogen-(C_1-C_6)-alkoxy, wherein n denotes an integer from 0, 1, 2 or 3. Preferably n is 1 or 2. Preferred compounds of formula I are those, wherein R^1 is halogen or halogen-(C_1-C_6)-alkyl. Especially preferred are those compounds of formula I, wherein R^1 is fluorine, chlorine or trifluoromethyl.

The compounds of general formula I can be manufactured by reacting a compound of formula



II

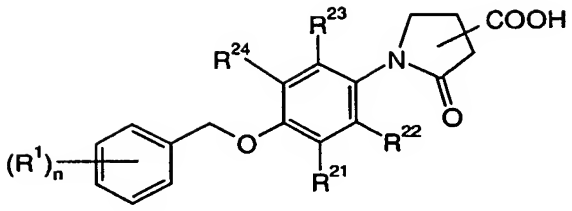
with an amine of formula H_2N-R^5 to obtain a compound of formula



Ia

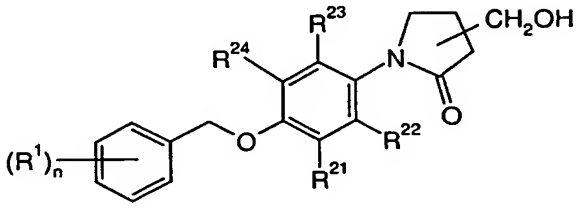
or, alternatively,

reducing a compound of formula



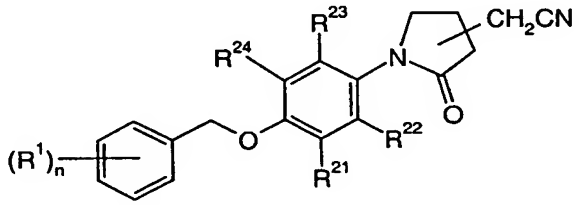
II

to the corresponding alcohol



III

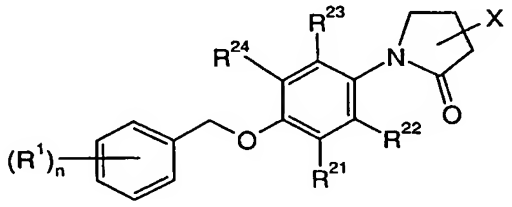
and reacting this compound with a cyanide salt to obtain a compound of formula



Ib

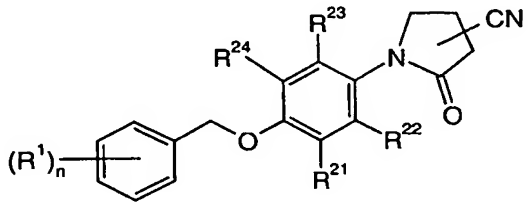
or, alternatively,

reacting a compound of formula



IV

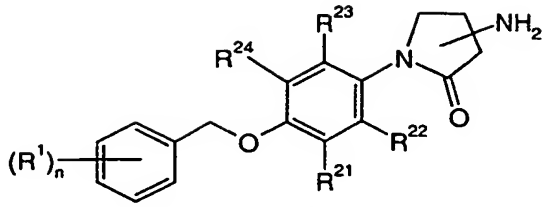
wherein X is halogen, with an cyanide salt, to obtain a compound of formula



Ic

or, alternatively,

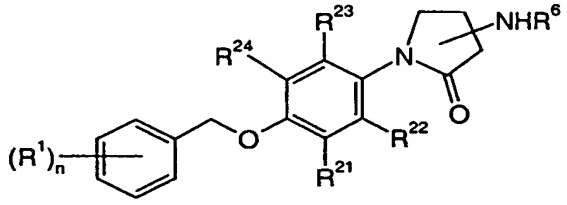
reacting a compound of formula



V

with an acylating agent of formula Y-CO-(C_1-C_6)-alkyl or Y'-SO_2-(C_1-C_6)-alkyl, wherein Y and Y' are representing suitably activating groups, e.g. halogens,

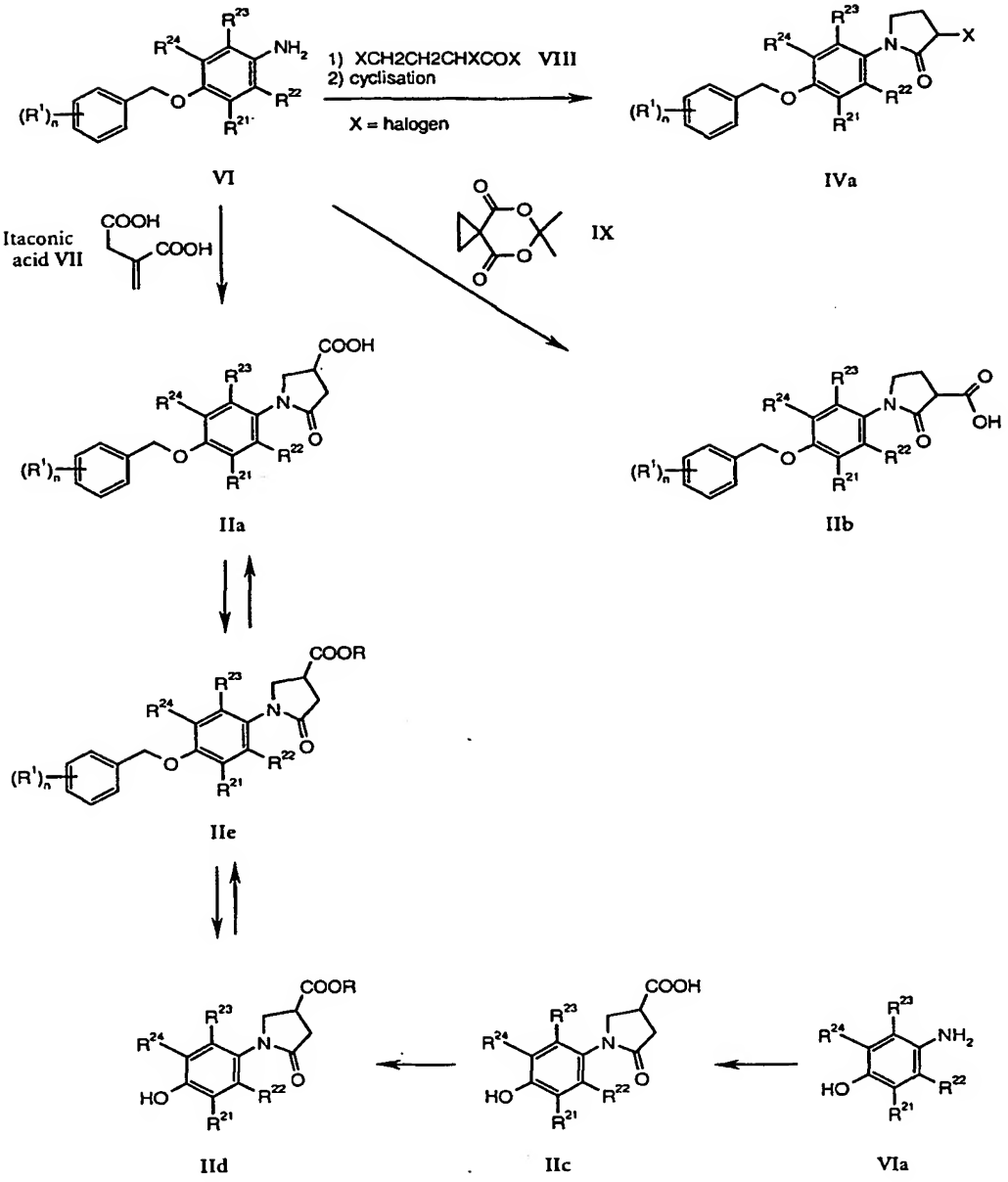
to obtain a compound of formula



Id

In accordance with the present invention, scheme 1 shows three main routes to compounds of the formula I, all starting from the key intermediate VI. The reaction of the intermediate VI with itaconic acid VII is preferentially done neat at temperatures between 80 °C and 200 °C. Preparation of the intermediates IVa is done by reacting VI with 2,4-dihalo-butyrylchlorides VIII (Ikuta et al., J. Med. Chem. 1987, 30, 1995), preferentially in inert solvents like dichloromethane, ethyl acetate or ethers in presence of a base like triethylamine or carbonate at 0 °C to 25 °C. Cyclisation of the intermediate 2,4-dihalo-N-acyl derivative to the pyrrolidone IVa is preferentially done with bases like sodium or potassium hydroxide in inert solvents like dichloromethane or ethers at 0 °C to 25 °C. Intermediates IIb are prepared by reacting VI with 6,6-dimethyl-5,7-dioxa-spiro[2,5]octane-4,8-dione, as described by Danishefsky et al., J. Amer.Chem. Soc. 1975, 97, 3239 (1975).

Scheme 1

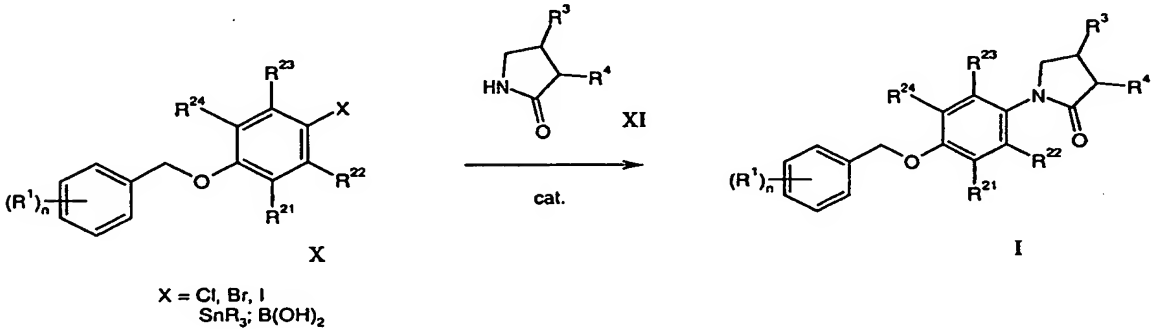


Furthermore, compounds of general formula IIa can be obtained starting with optionally substituted 4-amino-phenol VIa, its reaction with itaconic acid as described before, followed by esterification of the corresponding acid IIc following methods known per se and alkylation of the phenol IId. The alkylation of the phenolic alcohol is effected according to methods which are known per se in the presence of a base such as potassium carbonate. Chlorides, bromides, iodides, tosylates or mesylates come into consideration as alkylating agents. The reaction is effected in a solvent which is inert under the reaction conditions, such as e.g. acetone, methyl ethyl ketone, or N,N-dimethylformamide, at a temperature between about 0 °C and 120 °C. As an alternative approach, especially with regard to optically active pyrrolidinone derivatives, the Mitsunobu reaction of optionally

substituted benzylalcohols in inert solvents, such as e.g. diethyl ether or tetrahydrofurane, using dialkyl-azo-dicarboxylates in presence of phosphines leads to esters of formula IIe. In benzyl derivatives of formula IIe, especially those where n = 0, the benzyl group can be used as protecting group and, after its cleavage by hydrogenolysis, be replaced by differently substituted benzyl groups. To obtain acids of formula IIa, the corresponding esters of formula IIe can be hydrolysed by methods known per se using aqueous base or acid, preferably under acidic conditions in case of optically active pyrrolidinone derivatives.

Another method to prepare compounds of formula I involves cross-coupling reactions of arylstannanes (Lam et al., *Tetrahedron Lett.* 2002, 43, 3091), arylboronates (Lam et al., *Synlett* 2000, 5, 674); Chan et al., Tetrahedron Lett. 1998, 39, 2933) or aryl halides (Buchwald et al., *J. Amer. Chem. Soc.* 1996, 118, 7215) with the corresponding pyrrolidones (scheme 2).

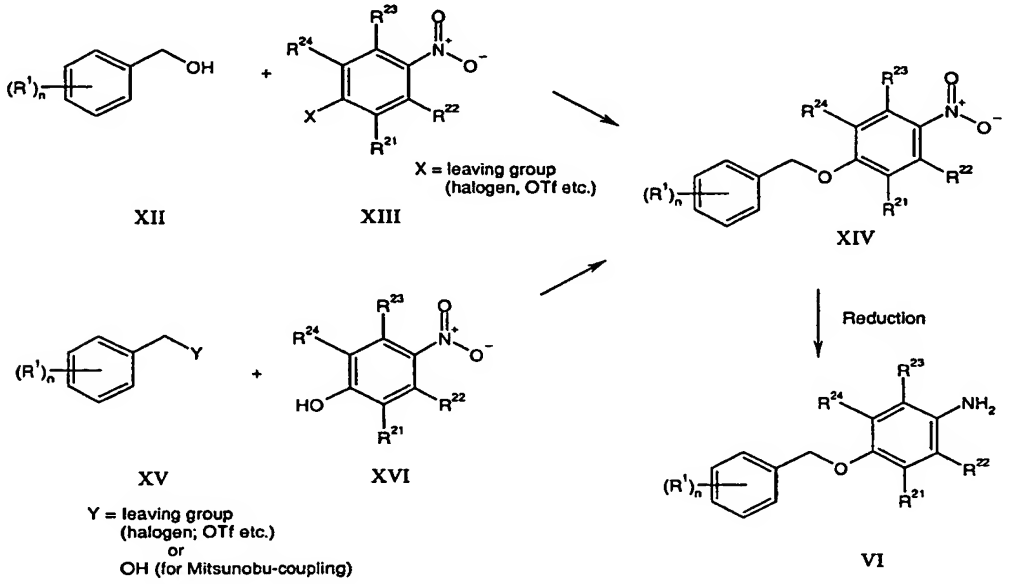
Scheme 2



In accordance with the present invention, a possibility to prepare compounds of general formula VI is shown in scheme 3: The intermediates XIV are accessible through nucleophilic substitution of aromatic nitro compounds XIII containing p-substituted leaving groups with benzylic alcohols XII. Leaving groups in para-position can be for example halogens (F, Cl, Br, I), tosylates, mesylates or triflates. These substitution reactions can be conducted neat or in inert solvents like for example toluene or xylene. Preferred reaction temperatures are between 50 °C and 150 °C. Alternatively, compounds XIV can be prepared by Williamson-ether synthesis, starting from p-nitrophenols XVI and benzylic halides, tosylates, mesylates or triflates XV. Bases used can be for example alcoholates or carbonates (sodium, potassium or cesium carbonate). Preferred solvents are lower alcohols, acetonitrile or lower ketones at temperatures between 20 °C and reflux temperature. Another approach is the Mitsunobu-coupling of benzylic alcohols with p-nitrophenols. The reaction is done as usual in inert solvents like for example diethyl ether or tetrahydrofurane, using dialkyl-azo-dicarboxylates in presence of phosphines (for example tributyl- or triphenyl-phosphine).

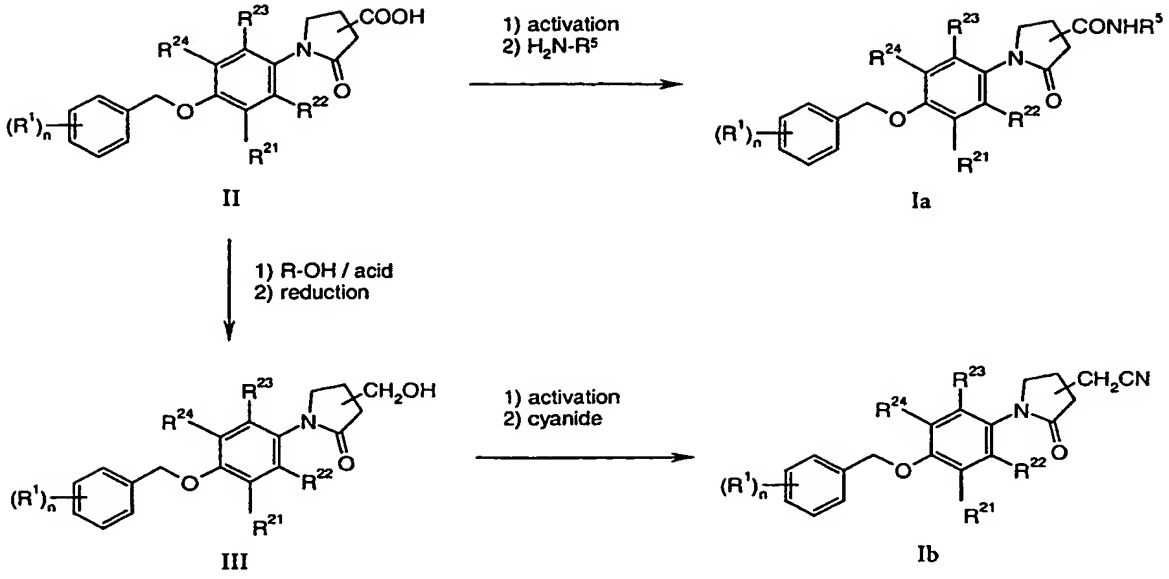
The key intermediates XIV are reduced to the amino-compounds VI using catalytic hydrogenation (for example platinum on charcoal in lower alcohols, ethyl acetate or tetrahydrofurane). An alternative is the reduction of the nitro-group by metals like iron, tin, or zinc in acidic media like diluted hydrochloric acid or acetic acid. Metals can also be replaced by metal salts (for example tin-(II)-chloride).

Scheme 3



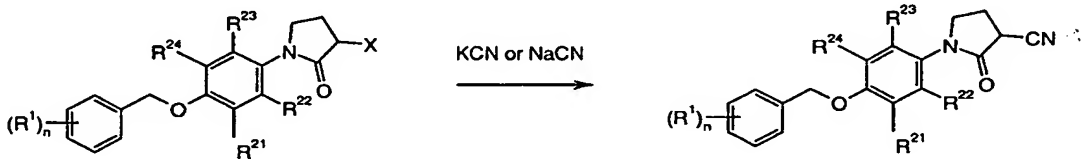
Intermediates II are transformed into compounds of formula I using standard procedures (scheme 4). The acids II are activated via acid chloride (thionyl chloride or oxalyl chloride) or with DCC, EDC etc. and subsequently coupled with the amine R^5NH_2. Alternatively, II can be reduced to the intermediate III. This is preferentially done by first converting the acids II into their esters (alcohol / acid catalysis) and reduction with reagents like sodium borohydride in solvents like tetrahydrofurane at 20 °C to 65 °C. Activation of the alcohol III via mesylate or triflate and reaction with sodium or potassium cyanide at 40 °C to 80 °C leads to the desired nitriles of formula Ib.

Scheme 4



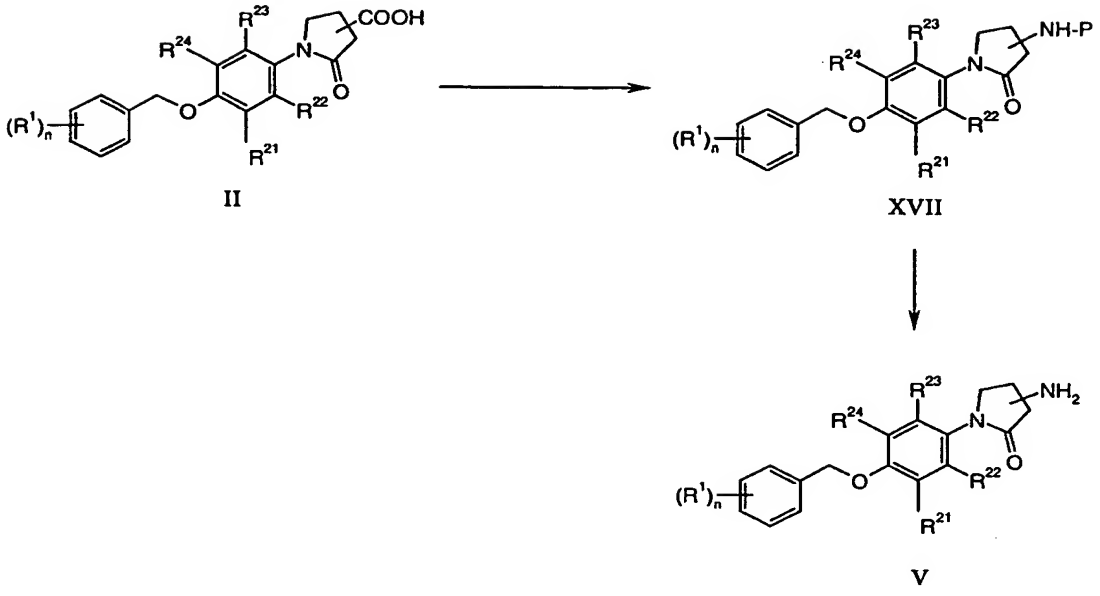
Intermediates IVa can be transformed into the desired compounds Ica by reaction with sodium or potassium cyanide in solvents like N,N-dimethylformamide, acetone or acetonitrile at 20 °C to 140 °C. Catalytic amounts of sodium or potassium iodide can be added to speed up the reaction (scheme 5).

Scheme 5



Compounds of formula V can be obtained starting from acid derivatives of formula II by nucleophilic migrations from a carbon to a nitrogen atom, such as e.g. by Hofmann or Curtius rearrangement, via the formation of the corresponding isocyanate and its treatment with suitable alcohols delivering the protected amino group, methods known per se from the literature (scheme 6). For the treatment of the intermediate isocyanate, alcohols are selected which yield the typical carbamates used as amine protecting groups, such as e.g. tert-butoxycarbonyl, benzyloxycarbonyl, or fluorenylmethoxycarbonyl. Their cleavage to the amine follow the protocols which are well known in the literature. The further transformation to compounds of formula I can be performed by standard procedures, such as e.g. by reaction with activated acyl derivatives, e.g. acyl halogenides or anhydrides, or by condensation reactions of the acid using e.g. carbodiimides as condensation reagent.

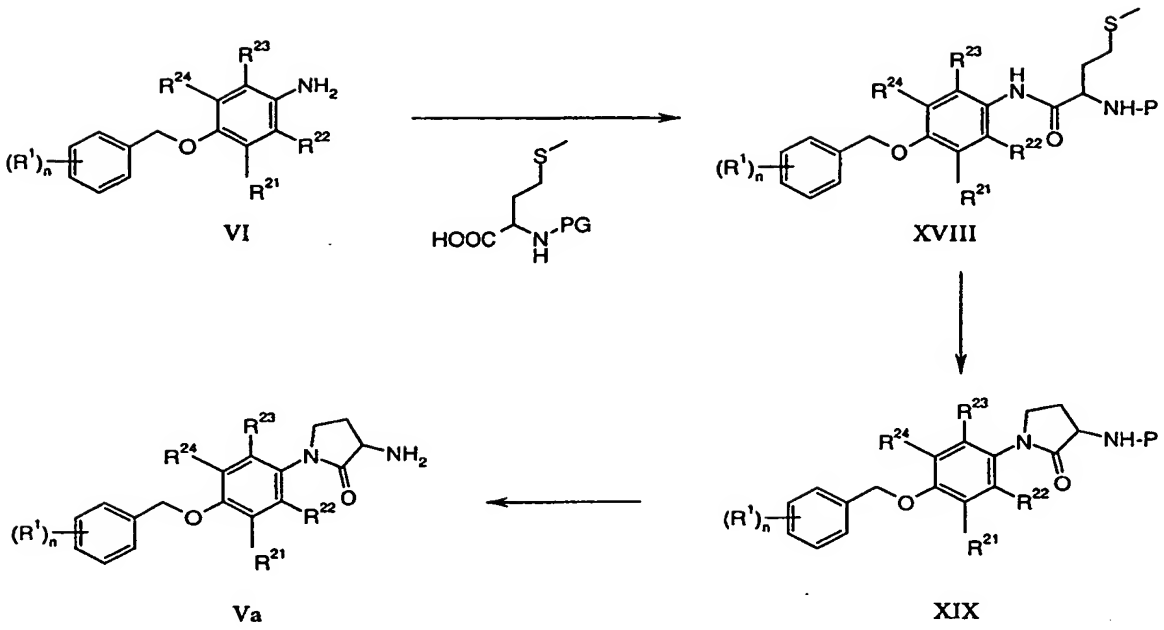
Scheme 6



II XVII V

For the preparation of 3-amino-1-(4-benzyloxy-phenyl)-pyrrolidin-2-one derivatives of formula Va, especially with regard to the synthesis of enantiomerically enriched intermediates of formula Va, an alternative route can be followed (scheme 7). Basically, the protocol follows the conditions described by R. M. Freidinger et al. in *J. Org. Chem.* 1982, 47, 104-109, where the aniline derivative of formula VI is acylated by an N-protected methionine derivative in its racemic or optically active form by standard conditions of condensation reactions. Methylation with methyliodide or trimethylsulfonium- or trimethylsulfoxonium salts and treatment of the resulting dimethylsulfonium salt with base, such as e.g. sodium hydride or lithium or potassium bis(trimethylsilyl)amide, in solvents inert under these conditions, e.g. tetrahydrofurane, dichloromethane or N,N-dimethylformamide, yield the cyclised N-protected product of formula Va. Another variation of this cyclisation procedure is described in European patent application EP 0 985 665 A1 which refers to a process for the preparation of 3-amino-2-oxo-pyrrolidines.

Scheme 7



Compounds of general formula I can also exist in optical pure form. Separation into antipodes can be affected according methods known per se, either preferably at an early stage of the synthesis starting with compounds of formula II by salt formation with an optically active amine such as, for example, (+)- or (-)-1-phenylethylamine and separation of the diastereomeric salts by fractional crystallisation or preferably by derivatisation with a chiral auxiliary substance such as, for example, (+)- or (-)-2-butanol, (+)- or (-)-1-phenylethanol, or (+)- or (-)-menthol and separation of the diastereomeric products by chromatography and/or crystallisation and subsequent cleavage of the bond to the chiral auxiliary substance. In order to determine the absolute configuration of the pyrrolidinone derivative obtained, the pure diastereo-meric salts and derivatives can be analysed by conventional spectroscopic methods, with X-ray spectroscopy on single crystals being an especially suitable method.

The compounds of formula I are, as already mentioned above, monoamine oxidase B inhibitors and can be used for the treatment or prevention of diseases in which MAO-B inhibitors might be beneficial. These include acute and chronic neurological disorders, cognitive disorders and memory deficits. Treatable neurological disorders are for instance traumatic or chronic degenerative processes of the nervous system, such as Alzheimer's disease, other types of dementia, minimal cognitive impairment or Parkinson's disease. Other indications include psychiatric diseases such as depression, anxiety, panic attack, social phobia, schizophrenia, eating and metabolic disorders such as obesity as well as the prevention and treatment of withdrawal syndromes induced by abuse of alcohol, nicotine

and other addictive drugs. Other treatable indications may be reward deficiency syndrome (G.M. Sullivan, International patent application No. WO 01/34172 A2), peripheral neuropathy caused by cancer chemotherapy (G. Bobotas, International Patent Application No. WO 97/33572 A1), or the treatment of multiple sclerosis (R.Y. Harris, International patent application No. WO 96/40095 A1) and other neuroinflammatory diseases.

The compounds of formula I are especially useful for the treatment and prevention of Alzheimer's disease and senile dementia.

The pharmacological activity of the compounds was tested using the following method:

The cDNA's encoding human MAO-A and MAO-B were transiently transfected into EBNA cells using the procedure described by E.-J. Schlaeger and K. Christensen (Transient Gene Expression in Mammalian Cells Grown in Serum-free Suspension Culture; Cytotechnology, 15: 1-13, 1998). After transfection, cells were homogenised by means of a Polytron homogenizer in 20 mM Tris HCl buffer, pH 8.0, containing 0.5 mM EGTA and 0.5 mM phenylmethanesulfonyl fluoride. Cell membranes were obtained by centrifugation at 45,000 x *g* and, after two rinsing step with 20 mM Tris HCl buffer, pH 8.0, containing 0.5 mM EGTA, membranes were eventually re-suspended in the above buffer and aliquots stored at -80 °C until use.

MAO-A and MAO-B enzymatic activity was assayed in 96-well-plates using a spectrophotometric assay adapted from the method described by M. Zhou and N. Panchuk-Voloshina (A One-Step Fluorometric Method for the Continuous Measurement of Monoamine Oxidase Activity, Analytical Biochemistry, 253: 169–174, 1997). Briefly, membrane aliquots were incubated in 0.1 M potassium phosphate buffer, pH 7.4, for 30 min at 37 °C with or without various concentrations of the compounds. After this period, the enzymatic reaction was started by the addition of the MAO substrate tyramine together with 1 U/ml horse-radish peroxidase (Roche Biochemicals) and 80 µM *N*-acetyl-3,7-dihydroxyphenoxazine (Amplex Red, Molecular Probes). The samples were further incubated for 30 min at 37 °C in a final volume of 200 µl and absorbance was then determined at a wavelength of 570 nm using a SpectraMax plate reader (Molecular Devices). Background (non-specific) absorbance was determined in the presence of 10 µM clorgyline for MAO-A or 10 µM L-deprenyl for MAO-B.

IC_{50} values were determined from inhibition curves obtained using nine inhibitor concentrations in duplicate, by fitting data to a four parameter logistic equation using a computer program.

The compounds of the present invention are specific MAO-B inhibitors. The IC_{50} values of preferred compounds of formula I as measured in the assay described above are in the range of 1 μM or less, typically 0.1 μM or less, and ideally 0.02 μM or less.

The compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They may also contain other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula I and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being

weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Example 1

(RS)-1-(4-Benzyloxy-phenyl)-2-oxo-pyrrolidine-3-carbonitrile

a) (RS)-N-(4-Benzyloxy-phenyl)-2,4-dibromo-butyramide

A solution of 12.8 g (64.2 mmol) 4-benzyloxyaniline and 9.74 g (96.3 mmol) triethylamine in 125 ml dichloromethane is cooled to 0 °C. 20.4 g (77.1 mmol) of 2,4-dibromobutyryl chloride (Ikuta et al., J. Med. Chem. 1987, 30, 1995) is slowly added over a period of 45 min. The reaction mixture is stirred for additional 15 min., then hydrolysed with 100 ml of water. The insoluble precipitate is filtered off and the organic phase is washed successively with a saturated solution of sodium hydrogencarbonate and water. After drying and evaporation, the crude product is subjected to chromatography (silica gel, dichloromethane) to yield 6.1 g (22 %) of a colorless solid. Mp = 139.5-142 °C.

b) (RS)-1-(4-Benzyloxy-phenyl)-3-bromo-pyrrolidin-2-one

6.1 g (14.3 mmol) (RS)-N-(4-benzyloxy-phenyl)-2,4-dibromo-butyramide and 0.1 g of Dowex 2X10 are suspended in 50 ml dichloromethane 7 ml of a 50% aqueous sodium hydroxide solution is slowly added under vigorous stirring. The resulting reaction mixture is stirred overnight at room temperature, then poured into 25 ml of cold water. The organic phase is separated, dried and evaporated. The crude material is recrystallised from ethyl acetate to yield 1.72 g (35 %) of a brownish solid. Mp = 125-126 °C.

c) (RS)-1-(4-Benzyloxy-phenyl)-2-oxo-pyrrolidine-3-carbonitrile

300 mg (0.87 mmol) of (RS)-1-(4-benzyloxy-phenyl)-3-bromo-pyrrolidin-2-one is dissolved in 5 ml N,N-dimethylformamide. 64 mg (1.3 mmol) sodium cyanide and 13 mg (0.09 mmol) sodium iodide are added and the suspension stirred for 10 min. at 120 °C. The reaction mixture is treated with water and extracted with ethyl acetate to yield 33 mg (13 %) of a colorless solid. MS: m/e = 293.3 $(M+H)^+$.

Example 2

(RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

a) (RS)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid

18.8 g (94.4 mmol) 4-benzyloxyaniline are mixed with 12.28 g (94.4 mmol) itaconic acid. The mixture is heated to 130 °C. After 20 min. the melted material solidifies. The resulting solid is triturated with ethyl acetate to yield 28.26 g (96 %) of greyish solid. MS: m/e = 311 (M^+).

b) (RS)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methyl ester

7.46 g (24 mmol) (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid is dissolved in a mixture of 40 ml dichloromethane and 7.5 ml methanol. 0.13 ml concentrated sulfuric acid is added and the reaction mixture hold under reflux over night. The solvent is evaporated and the residue triturated with diethyl ether to yield 7.26 g (93%) of a colorless solid (used in the next step without further purification).

c) (RS)-1-(4-Hydroxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methyl ester

7.26 g (22.3 mmol) (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methyl ester is dissolved in 200 ml tetrahydrofuran. After addition of 726 mg palladium 10% on charcoal hydrogenation is performed at room temperature and normal pressure. After 3 hours, the catalyst is filtered off and the solvent evaporated to yield 6.04 g of crude product (used in the next step without further purification).

d) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester

6.04 g (RS)-1-(4-hydroxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methyl ester, 7.10 g (51.4 mmol) potassium carbonate and 5.34 g 3-fluorobenzyl bromide are suspended in 250 ml ethyl methyl ketone. The reaction mixture is heated at 90 °C for 5 hours, cooled and poured into water. Extraction with ethyl acetate gives a crude material which is subjected to chromatography (silica gel, n-hexane / ethyl acetate 1:1). This gives 2.10 g (24 %) of a colorless solid. MS: m/e = 344.3 $(M+ H)^+$.

e) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

300 mg (0.87 mmol) (RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester is dissolved in a mixture of 1 ml N,N-dimethylformamide and 0.18 ml of a 33 % solution of methylamine in ethanol. The reaction vessel is tightly stopped and hold at 120 °C for 48 hours. Water is added and the product extracted with ethyl acetate. Drying and evaporation yields 92 mg (31 %) of a slightly yellowish product. MS: m/e = 343.3 $(M + H)^+$.

The compounds of Examples 3 to 7 are obtained in an analogous manner to that described in Example 2d) and e), starting from (RS)-1-(4-hydroxyphenyl)-5-oxo-pyrrolidine-3-carboxylic acid methyl ester [Example 2c)] by alkylation of the phenol and subsequent aminolysis of the ester:

Example 3

(RS)-[1-[4-(3,4-Difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared by alkylation with 3,4-difluorobenzyl bromide to obtain the (RS)-1-[4-(3,4-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester as a colorless solid [85% of theory; MS: m/e = 362.2 $(M^+ + H)$] and, thereupon, treatment with methylamine to yield the (RS)-[1-[4-(3,4-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide. Yield : 7 % of a colorless solid. MS: m/e = 361 $(M+ H)^+$.

Example 4

(RS)-[1-[4-(2,6-Difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared by alkylation with 2,6-difluorobenzyl bromide to obtain the (RS)-1-[4-(2,6-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester as a yellowish oil and, thereupon, treatment with methylamine in ethanol at 80 °C during 18 h to yield the (RS)-[1-[4-(2,6-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide. Yield : 33 % of a colorless solid. MS: m/e = 361 $(M+ H)^+$.

Example 5

(RS)-1-[4-(3-Methoxy-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared by alkylation with 3-methoxybenzyl bromide to obtain the (RS)-1-[4-(3-methoxy-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester as a yellowish oil and, thereupon, treatment with methylamine in ethanol at 80 °C during 18 h to yield the (RS)-1-[4-(3-methoxy-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide. Yield : 75 % of a colorless solid. MS: m/e = 355 $(M+ H)^+$.

Example 6

(RS)-5-Oxo-1-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared by alkylation with 3-(trifluoromethyl)benzyl chloride to obtain the (RS)-5-oxo-1-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid methyl ester as a yellowish solid and, thereupon, treatment with methylamine in ethanol at 80 °C during 18 h to yield the (RS)-5-oxo-1-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid methylamide. Yield : 54 % of a colorless solid. MS: m/e = 393 $(M+ H)^+$.

Example 7

(RS)-1-[4-(3-Chloro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared by alkylation with 3-chlorobenzyl chloride to obtain the (RS)-1-[4-(3-chloro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester as a colorless solid and, thereupon, treatment with methylamine in ethanol at 80 °C during 18 h to yield the (RS)-1-[4-(3-chloro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide. Yield : 73 % of a colorless solid. MS: m/e = 359 $(M+ H)^+$.

Example 8

(RS)-1-[4-(3,4-Difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetonitrile

a) (RS)-1-[4-(3,4-Difluoro-benzyloxy)-phenyl]-4-hydroxymethyl-pyrrolidin-2-one

2.0 g (5.54 mmol) (RS)-1-[4-(3,4-Difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester is dissolved in 50 ml tetrahydrofurane. 1.05 g (27.7 mmol) of sodium borohydride is added and the reaction mixture boiled under reflux for 24 hours. Water is added and the product is extracted with ethyl acetate to yield 1.68 g (91%) of a yellowish solid. MS: m/e = 334.3 $(M+ H)^+$.

b) (RS)-1-[4-(3,4-Difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetonitrile

300 mg (0.9 mmol) (RS)-1-[4-(3,4-Difluoro-benzyloxy)-phenyl]-4-hydroxymethyl-pyrrolidin-2-one and 0.136 mg (1.35 mmol) triethylamine are dissolved in 20 ml dichloromethane and cooled to 0 °C. 155 mg (1.35 mmol) methanesulfonyl chloride is added. The mixture is stirred at 0 °C for 30 min. then at room temperature for 3 hours, then washed successively with water, 1 M hydrochloric acid, 10% sodium hydrogen carbonate and saturated sodium chloride solution. Drying and evaporation gives the crude mesylate, which is dissolved in 2 ml N,N-dimethylformamide. 110 mg (2.25 mmol) sodium cyanide is added and the reaction mixture is hold at 100 °C for 24 hours. Hydrolysis and extraction with ethyl acetate gives the crude nitrile, which is subjected to chromatography (silica gel, dichloromethane / methanol). Yield : 20 % of a brownish solid. MS: m/e = 343.1 $(M+ H)^+$.

Example 9

(RS)-{1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetonitrile

a) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-4-hydroxymethyl-pyrrolidin-2-one

The title compound is prepared in analogy to Example 8 a) from (RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester and sodium borohydride. Yield : 82 % of a colorless solid. MS: m/e = 316.3 $(M+ H)^+$.

b) (RS)-{1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetonitrile

The title compound is prepared in analogy to Example 8 b) from (RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-4-hydroxymethyl-pyrrolidin-2-one, methanesulfonyl chloride and sodium cyanide. Yield : 27 % of a colorless solid. MS: m/e = 325.2 $(M+ H)^+$.

Example 10

(RS)-1-[3-Fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

a) 2-Fluoro-1-(3-fluoro-benzyloxy)-4-nitro-benzene

A mixture of 10.0 g (63.7 mmol) 2-fluoro-4-nitrophenol, 17.6 g (127 mmol) potassium carbonate and 13.24 g (70.0 mmol) 3-fluorobenzyl bromide in 200 ml ethyl methyl ketone is hold overnight at 80 °C. The reaction mixture is diluted with water and extracted with ethyl acetate. Crystallisation from diethyl ether / n-hexane gives 12.68 g (75 %) of a slightly yellow solid. MS: m/e = 265.1 (M^+).

b) 3-Fluoro-4-(3-fluoro-benzyloxy)-phenylamine

12.68 g (47.8 mmol) 2-fluoro-1-(3-fluoro-benzyloxy)-4-nitro-benzene is dissolved in 150 ml ethyl acetate. 1.27 g platinum 5 % on charcoal is added and the mixture is hydrogenated at room temperature and normal pressure for 6 hours. The catalyst is filtered off and the solution evaporated to yield 11.03 g (98 %) of a dark brown liquid. MS: m/e = 235.1 (M^+).

c) (RS)-1-[3-Fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid

The title compound is prepared in analogy to Example 2 a) from 3-fluoro-4-(3-fluoro-benzyloxy)-phenylamine and itaconic acid. Yield : 86 % of a colorless solid. MS: m/e = 346.1 (M-H).

d) (RS)-1-[3-Fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

500 mg (1.44 mmol) (RS)-1-[3-fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid is suspended in 5 ml dichloromethane. 0.52 ml (7.2 mmol) thionyl chloride is added and the reaction mixture hold at 40 °C overnight. The solvent is evaporated and the crude acid chloride is again dissolved in 5 ml dichloromethane. 0.76 ml (7.2 mmol) of a 33% solution of methylamine in ethanol is added and the mixture heated to 40 °C for 6 hours. Water is added and the product is extracted with ethyl acetate. Chromatography (silica gel, dichloromethane / methanol) yields 348 mg (67 %) of a pink solid. MS: m/e = 361.2 $(M+ H)^+$.

Example 11

(RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid methylamide

a) 1-(4-Benzyloxy-phenyl)-pyrrolidin-2-one

20.3 g (101.9 mmol) 4-benzyloxyaniline and 9.1 ml (119.2 mmol) gamma-butyrolactone are treated with 3ml concentrated hydrochloric acid. The mixture is heated 20 hours to 160 °C, then 5.5 hours to 200 °C. After cooling, the mixture is extracted with 250 ml ethyl acetate, washed with saturated aqueous sodium hydrogencarbonate and dried. Evaporation of the solvent and recrystallisation from diethyl ether yields 8.4 g (31 %) of a brownish solid. MS: m/e = 267 (M^+).

b) 1-(4-Hydroxy-phenyl)-pyrrolidin-2-one

6.2 g (23.2 mmol) 1-(4-benzyloxy-phenyl)-pyrrolidin-2-one is dissolved in 200 ml tetrahydrofurane. 3 drops of acetic acid are added and the solution is hydrogenated for 5 hours at room temperature and normal pressure in presence of 0.62 g palladium 10 % on charcoal. Filtration and concentration gives a semisolid material. Chromatography (silica gel, dichloromethane / methanol 95 : 5) yields 2.73 g (66 %) of a brownish solid. MS: m/e = 175.9 (M-H).

c) 1-[4-(3-Fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one

The title compound is prepared in analogy to Example 2 d) from 1-(4-hydroxy-phenyl)-pyrrolidin-2-one and 3-fluoro-benzyl bromide. Yield : 88 % of a colorless solid. MS: m/e = 286.0 $(M+ H)^+$.

d) 1-[4-(3-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester

370 mg (15.4 mmol) sodium hydride is suspended in 20 ml tetrahydrofurane and 911 mg (7.7 mmol) diethylcarbonate is added. The suspension is heated to reflux temperature. A solution of 2.0 g (7.0 mmol) 1-[4-(3-Fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one in 10 ml tetrahydrofurane is slowly added into the boiling solution. The mixture is boiled for another 5 hours, then hydrolysed with cold water and washed successively with water, saturated sodium hydrogencarbonate solution, water and saturated sodium chloride solution. Chromatography (silica gel, dichloromethane / ethyl acetate) yields 1.3 g (52 %) of a yellowish semisolid. MS: m/e = 358.2 $(M+ H)^+$.

e) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid methylamide

300 mg (0.84 mmol) 1-[4-(3-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester is dissolved in 2 ml N,N-dimethylformamide. 0.17 ml (4.2 mmol) of a 33 % solution of methylamine in ethanol is added. The reaction vessel is tightly stoppered and heated to 120 °C for 24 hours. Addition of water precipitates the crude material. Chromatography (silica gel, dichloromethane / methanol) yields 41 mg (14 %) of a yellowish solid. MS: m/e = 343.2 $(M+ H)^+$.

Example 12

(RS)-1-[2-Fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

a) 2-Fluoro-4-(3-fluoro-benzyloxy)-1-nitro-benzene

The title compound is prepared in analogy to Example 10 a) from 3-fluoro-4-nitrophenol and 3-fluoro benzyl bromide. Yield : 100% of a colorless solid. MS: m/e = 265.0 (M^+).

b) 2-Fluoro-4-(3-fluoro-benzyloxy)-phenylamine

The title compound is prepared in analogy to Example 10 b) by hydrogenation of 2-fluoro-4-(3-fluoro-benzyloxy)-1-nitro-benzene. Yield : 98 % of a dark brown liquid. MS: m/e = 235.0 (M^+).

c) (RS)-1-[2-Fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid

The title compound is prepared in analogy to Example 10 c) from 2-fluoro-4-(3-fluoro-benzyloxy)-phenylamine and itaconic acid. Yield : 67 % of a purple solid. MS: m/e = 346.1 $(M+H)^+$.

d) (RS)-1-[2-Fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared in analogy to Example 10 d) from (RS)-1-[2-fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid and methylamine. Yield : 39 % of a brownish solid. MS: m/e = 361.2 $(M+H)^+$.

Example 13

(RS)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared in analogy to Example 10 d) from (RS)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid and methylamine. Yield : 73 % of a slightly yellow solid. MS: m/e = 325.4 $(M+H)^+$.

Example 14

(RS)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid amide

The title compound is prepared in analogy to Example 10 d) from (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid and ammonia. Yield : 95 % of a slightly brown solid. MS: m/e = 311.3 $(M+H)^+$.

Example 15

(RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid amide

a) (RS)-1-(4-Hydroxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid amide

420 mg (1.35 mmol) (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid amide is dissolved in a mixture of 15 ml tetrahydrofurane and 15 ml methanol. 70 mg of palladium 10 % on charcoal is added and the reaction mixture is hydrogenated over night at room temperature and normal pressure. Evaporation of the solvents yields 250 mg (84 %) of a brownish solid. MS: m/e = 221.2 $(M+H)^+$.

b) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid amide

The title compound is prepared in analogy to Example 2 d) from (RS)-1-(4-hydroxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid amide and 3-fluorobenzyl bromide. Yield : 60% of a colorless solid. MS: m/e = 328 (M^+).

Example 16

(RS)-[1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidin-3-yl]-acetonitrile

a) (RS)-1-(4-Benzyloxy-phenyl)-4-hydroxymethyl-pyrrolidin-2-one

The title compound is prepared in analogy to Example 8 a) from (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methyl ester and sodium borohydride. Yield : 82 % of a colorless solid. MS: m/e = 298.3 $(M+H)^+$.

b) (RS)-1-(4-Benzyloxy-phenyl)-4-chloromethyl-pyrrolidin-2-one

740 mg (2.49 mmol) (RS)-1-(4-benzyloxy-phenyl)-4-hydroxymethyl-pyrrolidin-2-one is dissolved in 20 ml toluene. 1.08 ml (14.9 mmol) thionyl chloride is added and the mixture refluxed for 6 hours. Evaporation and chromatography (silica gel, n-hexane / ethyl acetate 1:1) yields 123 mg (16 %) of a brownish semisolid. MS: m/e = 315.2 (M^+).

c) (RS)-[1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidin-3-yl]-acetonitrile

123 mg (0.39 mmol) (RS)-1-(4-benzyloxy-phenyl)-4-chloromethyl-pyrrolidin-2-one is dissolved in 2.5 ml N,N-dimethylformamide. After addition of 29 mg (0.58 mmol) sodium cyanide and 6 mg (0.04 mmol) sodium iodide, the mixture is hold at 120 °C for 15 min. Dilution with water and extraction with ethyl acetate yields 44 mg (37 %) of a brownish solid. MS: m/e = 307.3 $(M+H)^+$.

Example 17

(RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid amide

a) 1-(3-Fluorobenzyloxy)-4-nitro-benzene

A mixture of 5.04 g (40 mmol) 3-fluorobenzyl alcohol and 1.29 g (4mmol) tris-(dioxa-3,6-heptyl)amine is treated with 2.47 g (44 mmol) of potassium hydroxide. The mixture is stirred at room temperature for 10 min, then 5.55 g (44 mmol) of 4-fluoro-nitrobenzene is slowly added through a dropping funnel. The mixture is kept for 45 min at 80 °C, cooled to room temperature and diluted with about 75 ml water. Extraction with ethyl acetate and washing with 2M aqueous hydrochloric acid yields a yellowish organic phase, which is dried and evaporated. The residue is recrystallised from methanol to give 6.07 g (61 %) of the title compound. Yellow crystals, mp = 104-105 °C.

b) 4-(3-Fluoro-benzyloxy)-phenylamine

3 g (12.1 mmol) of 1-(3-fluorobenzyloxy)-4-nitro-benzene is dissolved in 125 ml of methanol. 150 mg of Pt 5% on charcoal is added and hydrogenation done under normal pressure for about 17 h. The catalyst is filtered and the solution evaporated to yield 2.51 g (95%) of crude brownish material. MS: m/e = 218.4 $(M+H)^+$.

c) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid

A solution of 561 mg (2.6 mmol) 4-(3-fluoro-benzyloxy)-phenylamine and 448 mg (2.6 mmol) 6,6-dimethyl-5,7-dioxa-spiro[2,5]octane-4,8-dione in 2ml dichloromethane is refluxed for 16 hours. 5 ml of diethylether is added and the precipitate filtered off to yield 485 mg (57 %) of a colorless solid. MS: m/e = 330.2 $(M+H)^+$.

d) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid amide

300 mg (0.91 mmol) (RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid is dissolved in 2 ml dichloromethane plus 2 drops of N,N-dimethyl-formamide. The solution is cooled to 0 °C and treated with 173 mg (1.37 mmol) oxalyl chloride. After 1 hour at 0 °C the solvent is removed under vacuum at room temperature. The residue is taken up in 1 ml dichloromethane and slowly added to a mixture of 2 ml tetrahydrofurane and 5 ml concentrated ammonia. Stirring is continued for 1 hour at room temperature. Evaporation of the solvents and dilution with water yields a precipitate, which is filtered off. Recrystallisation from methanol yields 112 mg (37 %) of a colorless solid. MS: m/e = 329.2 $(M+H)^+$.

Example 18

(RS)-1-[4-(4-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid amide

a) 1-(4-Fluorobenzyloxy)-4-nitro-benzene

The title compound is prepared in analogy to Example 17 a) from 4-fluorobenzyl alcohol and 4-fluoro-nitrobenzene. Yield : 86 % of a yellowish solid. Mp = 124-126 °C.

b) 4-(4-Fluoro-benzyloxy)-phenylamine

The title compound is prepared in analogy to Example 17 b) by reduction of 1-(4-fluorobenzyloxy)-4-nitro-benzene. Yield : 98 % of a red solid. MS: m/e = 218.3 $(M+H)^+$.

c) (RS)-1-[4-(4-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid

The title compound is prepared in analogy to Example 17 c) from 4-(4-fluoro-benzyloxy)-phenylamine and 6,6-dimethyl-5,7-dioxa-spiro[2,5]octane-4,8-dione. Yield : 56 % of a colorless solid. MS: m/e = 284.1 $(M-CO_2)$.

d) (RS)-1-[4-(4-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid amide

The title compound is prepared in analogy to Example 17 d) from (RS)-1-[4-(4-fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid and ammonia. Yield : 18% of a brownish solid. MS: m/e = 329.3 (M^++ H).

Example 19

(RS)-1-[4-(4-Fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared in analogy to Example 17 d) from (RS)-1-[4-(4-fluoro-benzyloxy)-phenyl]-2-oxo-pyrrolidine-3-carboxylic acid and methylamine. Yield : 17% of a colorless solid. MS: m/e = 343.2 $(M+H)^+$.

Example 20

(RS)-2-Oxo-1-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid amide

a) 1-(4-Trifluoromethyl-benzyloxy)-4-nitro-benzene

The title compound is prepared in analogy to Example 17 a) from 4-fluoro-nitro-benzene and 4-trifluoromethyl-benzyl alcohol. Yield 82 % of a slightly brown solid. Mp. = 80.5 – 81.5 °C.

b) 4-(4-Trifluoromethyl-benzyloxy)-phenylamine

The title compound is prepared in analogy to Example 17 b) by reduction of 1-(4-trifluoromethyl-benzyloxy)-4-nitro-benzene. Yield : 91 % of a yellowish solid. MS: m/e = 268.3 $(M+H)^+$.

c) (RS)-2-Oxo-1-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid

The title compound is prepared in analogy to Example 17 c) from 4-(4-trifluoro-methyl-benzyloxy)-phenylamine and 6,6-dimethyl-5,7-dioxa-spiro[2,5]octane-4,8-dione. Yield : 37 % of a colorless solid. MS: m/e = 380.1 $(M+H)^+$.

d) (RS)-2-Oxo-1-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid amide

150 mg (0.4 mmol) (RS)-2-oxo-1-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid is dissolved in 4 ml tetrahydrofurane. 59 mg (0.43 mmol) of

1-hydroxybenzotriazole and 80 mg (0.42 mmol) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide-hydrochloride is added and the reaction mixture is stirred at room temperature for 30 min. After cooling to 0 °C 4ml of concentrated ammonia is added and the resulting mixture stirred at room temperature for 1 hour. Dilution with water, extraction and chromatography (silica gel, ethyl acetate) yields 15 mg (10 %) of a colorless solid. MS: m/e = 379.2 $(M+H)^+$.

Example 21

(RS)-2-Oxo-1-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid methylamide

The title compound is prepared in analogy to Example 20 d) from (RS)-2-oxo-1-[4-(4-trifluoromethyl-benzyloxy)-phenyl]-pyrrolidine-3-carboxylic acid and methylamine. Yield : 6 % of a colorless solid. MS: m/e = 393.2 $(M+H)^+$.

Example 22

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

a) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid

3.5 g (10.2 mmol) of [Rac] 1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methyl ester (Example 2d) are dispersed in 11.2 ml of a 1N solution of sodium hydroxide, and tetrahydrofuran is added to such an extent that a clear solution is obtained. Thereupon, the reaction mixture is heated to 50 °C during 1 h. For the working-up, the cooled solution is treated with 11.2 ml of 1N hydrochloric acid and the tetrahydrofuran evaporated under reduced pressure while the product starts to precipitate. The product is filtered and dried under vacuum to yield 2.39 g (71% of theory) of a white solid which is used in the next step without further purification.

b) (RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-(3RS)-carbonyl chloride

A dispersion of 2.37 g (7.2 mmol) of (RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid in 50 ml of dichloromethane is treated with 3.1 ml (43.2 mmol) of thionylchloride at room temperature during 18 h. For the working-up, the reaction mixture is evaporated under reduced pressure to dryness, then the residue is dispersed in toluene and evaporated to dryness again to yield quantitatively the acid chloride as a yellowish solid which is used in the next step without further purification.

c) (3RS)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester

A solution of 2.49 g (7.2 mmol) of (RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-(3RS)-carbonyl chloride in 42 ml of dichloromethane is prepared and cooled to 0 °C. The solution of 0.73 g (6.0 mmol) of (R)-(+)-1-phenylethanol in a mixture of 10 ml of dichloromethane and 0.48 ml pyridine is added dropwise. After complete addition, the reaction mixture is warmed to room temperature and stirring continued for 20 min. For the working-up, the reaction mixture is evaporated under reduced pressure and 3.84 g of a yellowish solid residue are obtained. For purification, the material obtained is chromatographed on silica gel by flas-chromatography using a gradient of n-hexane to a 4:1 mixture of n-hexane and ethyl acetate as the eluent. There are obtained 1.96 g (76% of theory) of the mixture of the two diastereomers as a white solid. MS: m/e = 434 $(M+H)^+$.

d) (3R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester and
(3S)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester

The separation of 1.80 g (4.2 mmol) of the two isomers (Example 22c) is performed on a preparative chiral HPLC column (CHIRALPAK® AD, pressure: 17 bar, flow : 35 ml/min) using a 4:1 mixture of n-heptane and ethanol as the eluent. There are obtained 763 mg (42.4% of theory) of the first eluting isomer (3R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester [MS: m/e = 434 (M^+ + H)] and 860 mg (47.8% of theory) of the later eluting isomer (3S)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester [MS: m/e = 434 $(M+H)^+$], each as a white solid.

e) (R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid

A solution of 0.622 g (1.44 mmol) of (3R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester in 17 ml of dioxane is treated with 1.68 ml of hydrochloric acid (37%) and the mixture is heated to 50 °C during 18 h. For the work-up, the reaction mixture is evaporated under reduced pressure and the yellowish residue obtained is triturated with ethyl acetate at –10 °C. The mixture is filtered and the white solid dried under vacuum to yield 344 mg (73% of theory) of the (R)-acid which is used in the next step without further purification. MS: m/e = 328 $(M-H)^+$.

f) (R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

A solution of 0.339 g (1.03 mmol) of (S)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid in 21 ml of N,N-dimethylformamide, cooled to 0 °C, is treated consecutively with 0.15 ml (1.13 mmol) of triethylamine, 0.390 g (1.03 mmol) of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU), 0.085 g (1.24 mmol) of methylamine hydrochloride, and 0.15 ml (1.13 mmol) of triethylamine. The reaction is stopped after 30 min and the orange coloured solution is evaporated under reduced pressure. The residue obtained is triturated in ethyl acetate, the white solid product is filtered, thereafter dissolved in dichloromethane and the solution washed three times with water. The organic phase is dried over sodium sulfate, then evaporated under reduced pressure to yield 231 mg (66% of theory) of a white solid. MS: m/e = 343 $(M+H)^+$; $[\alpha]_{589}$ = -25.48° (c= 0.954, CH_2Cl_2).

Example 23

(S)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

a) (S)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid

In an analogous manner to that described in Example 22 e), starting from (3S)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester (Example 22d) by acidic hydrolysis of the ester there is obtained (S)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid as a white solid which is used in the next step without further purification. MS: m/e = 328 $(M-H)^+$.

b) (S)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide

In an analogous manner to that described in Example 22 f), by condensing (S)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid with methylamine using HBTU as the condensation agent there is obtained (S)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide as a white solid. MS: m/e = 343 $(M+H)^+$; $[\alpha]_{589}$ = +28.17° (c= 0.831, CH_2Cl_2).

Example 24

(R)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide

a) (RS)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carbonyl chloride

In an analogous manner to that described in Example 22 b), starting from (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (Example 2a) by treatment with thionylchloride there is obtained (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carbonyl chloride as a yellowish solid which is directly used in the next step without further purification.

b) (3R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester and
(3S)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester

In an analogous manner to that described in Example 22 c) and 22 d), starting from (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carbonyl chloride by reaction with (R)-(+)-1-phenylethanol there is obtained the mixture of the two isomers (3RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester which is separated on a preparative chiral HLPC column (conditions see Example 22 d) to yield the first eluting (3R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester [MS: m/e = 416 (M^+ + H)] and (3S)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester [MS: m/e = 416 $(M+H)^+$] as a white solid each.

c) (3R)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid

In an analogous manner to that described in Example 22 e), starting from (3R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester by acidic hydrolysis of the ester there is obtained (3R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid as a white solid which is used in the next step without further purification. MS: m/e = 310 $(M-H)^+$.

d) (R)-1-(4-Benzyloxy)-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide

In an analogous manner to that described in Example 22 f), by condensing (R)-1-(4-benzyloxy)-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid with methylamine using HBTU as the condensation agent there is obtained (R)-1-(4-benzyloxy)-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide as a white solid. MS: m/e = 325 $(M+H)^+$; $[\alpha]_{589}$ = -27.55° (c= 0.958, CH_2Cl_2).

Example 25

(S)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide

a) (RS)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carbonyl chloride

In an analogous manner to that described in Example 22 b), starting from (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (Example 2a) by treatment with thionylchloride there is obtained (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carbonyl chloride as a yellowish solid which is directly used in the next step without further purification.

b) (3R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester and
(3S)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester

In an analogous manner to that described in Example 18c and 18d, starting from (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carbonyl chloride by reaction with (R)-(+)-1-phenylethanol there is obtained the mixture of the two isomers (3RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester which is separated on a preparative chiral HLPC column (conditions see Example 18d) to yield the first eluting (3R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester [MS: m/e = 416 (M^+ + H)] and (3S)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester [MS: m/e = 416 $(M+H)^+$] as a white solid each.

c) (S)-1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid

In an analogous manner to that described in Example 18e, starting from (3S)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid (1R)-phenyl-ethyl ester (Example 20b) by acidic hydrolysis of the ester there is obtained (3S)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid as a white solid which is used in the next step without further purification. MS: m/e = 310 $(M-H)^+$.

d) (S)-1-(4-Benzyloxy)-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide

In an analogous manner to that described in Example 18f, by condensing (S)-1-(4-benzyloxy)-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid with methylamine using HBTU as the condensation agent there is obtained (S)-1-(4-benzyloxy)-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide as a white solid. MS: m/e = 325 $(M+H)^+$; $[\alpha]_{589}$ = +32.02° (c= 1.037, CH_2Cl_2).

Example 26

(RS)-N-{1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetamide

a) (RS)-[1-(4-Benzyloxy-phenyl)-5-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

A solution of 0.20 g (0.6 mmol) of (RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carbonyl chloride [Example 24a)] in 12 ml of toluene is cooled to 0 °C and 0.058 g (0.9 mmol) of sodium azide are added. The reaction mixture is warmed to room temperature and stirring continued or 1 h. Thereafter, the mixture is heated to 80 °C, 1.88 ml (20 mmol) of tert-butanol are added and stirring continued for 1 h. For the working-up, the mixture is cooled, diluted with ethyl acetate and, consecutively, extracted with saturated sodium hydrogencarbonate solution, water and brine. The organic phase is dried over sodium sulfate and evaporated under reduced pressure to yield the crude compound as a brownish solid. For purification, the material obtained is chromatographed on silica gel using a 2:1 mixture of n-hexane and ethyl acetate as the eluent. There are obtained 0.13 g (55% of theory) of (RS)-[1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester as a white solid. MS: m/e = 400 $(M + NH_4)^+$.

b) (RS)-[1-(4-Hydroxy-phenyl)-5-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

A solution of 82 mg (0.2 mmol) of (RS)-[1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester in 2 ml of tetrahydrofurane is hydrogenated in presence of 7 mg palladium on carbon (10%) at ambient pressure and room temperature during 18 h. For the working-up, the reaction mixture is filtered over Dicalit, then evaporated under reduced pressure. The crude (RS)-[1-(4-hydroxy-phenyl)-5-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester is obtained as a colorless oil, which is directly engaged in the next step without further purification and characterisation.

c) (RS)-{1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester

A solution of 62 mg (0.21 mmol) of the crude (RS)-[1-(4-hydroxy-phenyl)-5-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester in 3 ml of 2-butanone is treated with 0.031 ml (0.23 mmol) of 3-fluorobenzyl-bromide and 59 mg (0.42 mmol) of potassium carbonate and the mixture is stirred at 50 °C for 18 h. For the working-up, the reaction mixture is diluted with ethyl acetate and extracted with water. The organic phase is dried over sodium sulfate and evaporated under reduced pressure. For purification, the material obtained is chromatographed on silica gel using a 2:1 mixture of n-hexane and ethyl acetate as the eluent. There are obtained 61 mg (72% of theory) of (RS)-{1-[4-(3-fluoro-

benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester as a white solid. MS: m/e = 401 $(M+H)^+$.

d) (RS)-4-Amino-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one hydrochloride

A solution of 49 mg (0.12 mmol) of (RS)-{1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-carbamic acid tert-butyl ester in 1 ml of dioxane is treated with 0.10 ml of hydrochloric acid (37%). The yellowish solution is warmed to 45 °C for 1 h. For the working-up, the reaction mixture is evaporated under reduced pressure and the solid residue is triturated with ether. After filtration and drying, 33 mg (79% of theory) of (RS)-4-amino-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one hydrochloride are obtained as a white solid. MS: m/e = 301 $(M+H)^+$.

e) (RS)-N-{1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetamide

A solution of 25 mg (0.07 mmol) of (RS)-4-amino-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one hydrochloride in 1 ml of dichloromethane is treated with 22 µl (0.16 mmol) of triethylamine and cooled to 0 °C. To this solution, 6 µl (0.08 mmol) of acetylchloride are added and stirring at 0 °C is continued for 30 min. For the working-up, the reaction mixture is treated with 2 ml of ammonium hydroxide solution, the organic phase separated, thereafter dried over sodium sulfate and evaporated under reduced pressure. For purification, the material obtained is chromatographed on silica gel using a 95:5 mixture of dichloromethane and methanol as the eluent. There are obtained 20 mg (78% of theory) of (RS)-N-{1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetamide as a white solid. MS: m/e = 343 $(M+H)^+$.

Example 27

(S)-N-[1-(4-Benzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-acetamide

a) (S)-[1-(4-Benzyloxy-phenylcarbamoyl)-3-methylsulfanyl-propyl]-carbamic acid tert-butyl ester

A solution of 0.57 g (2.3 mmol) of (S)-Boc-methionine in 5 ml of dichloromethane is treated at room temperature consecutively with 0.87 g (2.3 mmol) of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (HBTU), 0.50 g (2.1 mmol) of 4-benzyloxyaniline hydrochloride and 0.98 ml (5.7 mmol) of N-ethyl-diisopropylamine. The reaction mixture is stirred during 1 h at room temperature. For the working-up, the reaction mixture is diluted with dichloromethane and treated with 20 ml of an aqueous solution of citric acid (10%). The aqueous phase is re-extracted with dichloromethane, the organic phases combined, dried over sodium sulfate and evaporated under reduced

pressure. For purification, the crude material obtained is chromatographed on silica gel using a 3:1 mixture of n-hexane and ethyl acetate as the eluent. There are obtained 0.74 g (82.5% of theory) of (S)-[1-(4-benzyloxy-phenylcarbamoyl)-3-methylsulfanyl-propyl]-carbamic acid tert-butyl ester as a white solid. MS: m/e = 431 $(M+H)^+$.

b) (S)-[1-(4-Benzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester

A mixture of 0.35 g (0.81 mmol) of (S)-[1-(4-benzyloxy-phenylcarbamoyl)-3-methylsulfanyl-propyl]-carbamic acid tert-butyl ester and 8.79 g (62.0 mmol) of methyliodide is stirred at room temperature for 3 d. Thereafter, the methyliodide is evaporated, the intermediate sulfonium salt dissolved in 15 ml of tetrahydrofurane and treated with 0.79 ml (0.79 ml) of lithium bis-(trimethylsilyl)amide (1 M solution in tetrahydrofurane) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture is evaporated under reduced pressure and the solid residue is directly submitted to chromatography on silica gel using a 2:1 mixture of n-hexane and ethyl acetate as the eluent. There are obtained 0.175 mg (56% of theory) of (S)-[1-(4-benzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester as a white solid. MS: m/e = 383 $(M+H)^+$.

c) (S)-3-Amino-1-(4-benzyloxy-phenyl)-pyrrolidin-2-one hydrochloride

A solution of 137 mg (0.36 mmol) of (S)-[1-(4-benzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-carbamic acid tert-butyl ester in 2 ml of dioxane is treated with 0.3 ml of hydrochloric acid (37%). The solution is warmed to 45 °C for 1 h forming a white suspension. For the working-up, the reaction mixture is evaporated under reduced pressure and the solid residue is triturated with a small volume of methanol. After filtration and drying, 94 mg (82% of theory) of (S)-3-amino-1-(4-benzyloxy-phenyl)-pyrrolidin-2-one hydrochloride are obtained as a white solid. MS: m/e = 283 $(M + H)^+$.

d) (S)-N-[1-(4-Benzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-acetamide

A solution of 40 mg (0.13 mmol) of (S)-3-amino-1-(4-benzyloxy-phenyl)-pyrrolidin-2-one hydrochloride in 2 ml of dichloromethane is treated with 38 µl (0.28 mmol) of triethylamine and cooled to 0 °C. To this solution, 10 µl (0.14 mmol) of acetylchloride are added and stirring at 0 °C is continued for 30 min. For the working-up, the reaction mixture is treated with 2 ml of ammonium hydroxide solution, the organic phase separated, thereafter dried over sodium sulfate and evaporated under reduced pressure. For purification, the material obtained is chromatographed on silica gel using a 95:5 mixture of dichloromethane and methanol as the eluent. There are obtained 31 mg (76% of theory) of (S)-N-[1-(4-enzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-acetamide as a white solid. MS: m/e = 325 $(M+H)^+$.

Example 28

(S)-N-[1-(4-Benzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-methanesulfonamide

In an anologous manner to that described in Example 27 d), the reaction of (S)-3-amino-1-(4-benzyloxy-phenyl)-pyrrolidin-2-one hydrochloride with methanesulfochloride in the presence of triethylamine yields the (S)-N-[1-(4-benzyloxy-phenyl)-2-oxo-pyrrolidin-3-yl]-methanesulfonamide as a white solid. MS: m/e = 361 $(M+H)^+$.

Example A

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

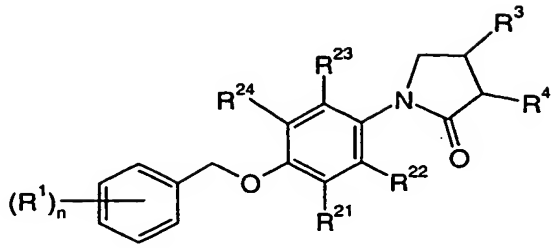
Example D

An injection solution may have the following composition and is manufactured in usual manner:

Active substance	1.0 mg
1 N HCl	20.0 µl
acetic acid	0.5 mg
NaCl	8.0 mg
phenol	10.0 mg
1 N NaOH	q.s. ad pH 5
H_2O	q.s. ad 1 ml

Claims

1. Compounds of the general formula



I

wherein

R^1 is halogen, halogen-(C_1-C_6)-alkyl, cyano, C_1-C_6-alkoxy or halogen-(C_1-C_6)-alkoxy;

R^{21}, R^{22}, R^{23} and R^{24} independently from each other are selected from the group consisting of hydrogen and halogen;

either

R^3 is –$CONHR^5$, -CH_2CN, -CN or –NHR^6, and R^4 is hydrogen;

or

R^3 is hydrogen, and R^4 is –$CONHR^5$, -CH_2CN, -CN or –NHR^6;

R^5 is hydrogen or C_1-C_3-alkyl;

R^6 is –CO-(C_1-C_6)-alkyl or -SO_2-(C_1-C_6)-alkyl; and

n is 0, 1, 2 or 3;

as well as individual isomers, racemic or non-racemic mixtures thereof.

2. Compounds of formula I according to claim 1, wherein R^3 is –$CONHR^5$, -CH_2CN, or -CN, and R^4 is hydrogen.

3. Compounds of formula I according to claim 2, wherein R^3 is –$CONHR^5$ and R^5 is hydrogen or C_1-C_3-alkyl.

4. Compounds of formula I according to claim 3, wherein R^5 is hydrogen.

5. A compound of formula 1 according to claim 4, which compound is (RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid amide.

6. Compounds of formula I according to claim 3, wherein R^5 is methyl.

7. Compounds of formula I according to claim 6, which compounds are selected from the group consisting of
(RS)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-[1-[4-(3,4-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-[1-[4-(2,6-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-[4-(3-chloro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-[3-fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-[2-fluoro-4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methylamide,
(RS)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide, and
(R)-1-(4-benzyloxy-phenyl)-5-oxo-pyrrolidine-3-carboxylic acid methylamide.

8. Compounds of formula I according to claim 2, wherein R^3 is $-CH_2CN$.

9 A compound of formula I according to claim 8, which compound is
(RS)-1-[4-(3,4-difluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetonitrile.

10. Compounds of formula I according to claim 1, wherein R^3 is hydrogen, and R^4 is $-CONHR^5$, $-CH_2CN$, or -CN.

11. Compounds of formula I according to claim 10, wherein R^4 is $-CONHR^5$.

12. Compounds of formula I according to claim 10, wherein R^4 is $-CN$.

13. A compound of formula I according to claim 12, which compound is
(RS)-1-(4-benzyloxy-phenyl)-2-oxo-pyrrolidine-3-carbonitrile.

14. Compounds of formula I according to claim 1, wherein R^3 is $-NHR^6$, and R^4 is hydrogen.

15. A compound of formula I according to claim 14, which compound is
(RS)-N-{1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-acetamide.

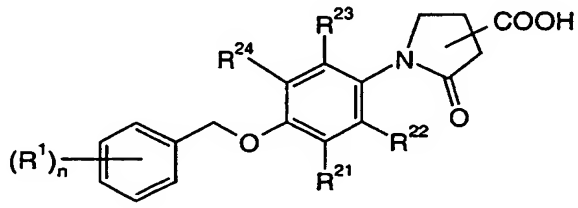
16. Compounds of formula I according to claim 1, wherein R^3 is hydrogen, and R^4 is $-NHR^6$.

17. Compounds of formula I according to claim 1, wherein n is 1 or 2.

18. Compounds of formula I according to claim 17, wherein R^1 is halogen or halogen-(C_1-C_6)-alkyl.

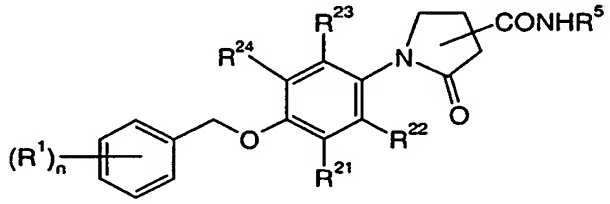
19. A process for the manufacture of a compound of formula I according to any one of claims 1 to 18, which process comprises

a) reacting a compound of formula



II

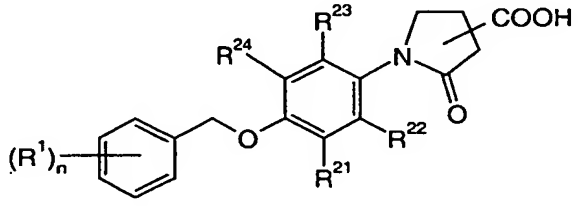
with an amine of formula H_2N-R^5 to obtain a compound of formula



Ia

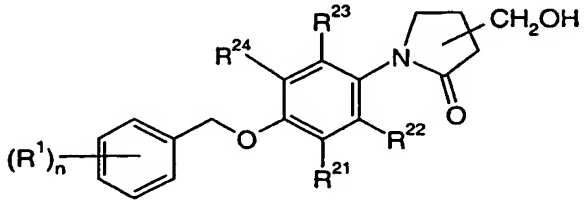
or

b) reducing a compound of formula



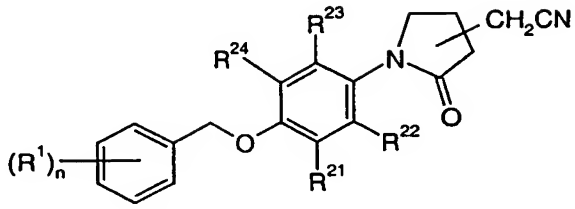
II

to the corresponding alcohol



III

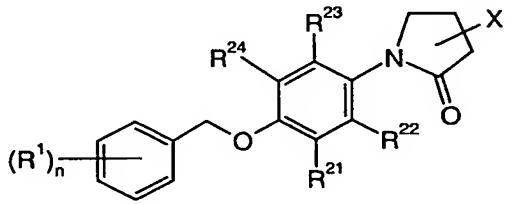
and reacting this compound with a cyanide salt
to obtain a compound of formula



Ib

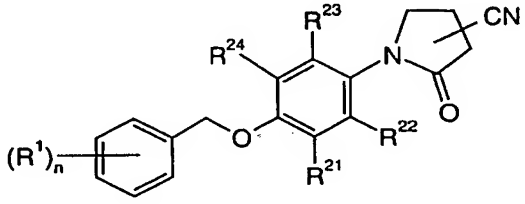
or

c) reacting a compound of formula



IV

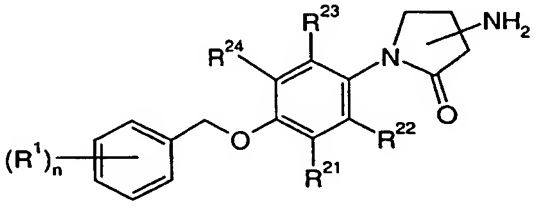
wherein X is halogen, with an cyanide salt,
to obtain a compound of formula



Ic

or

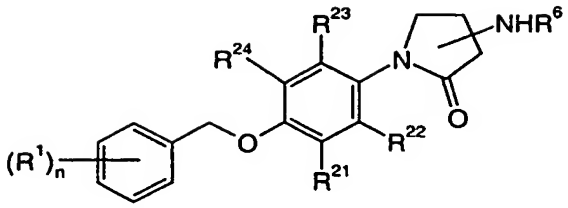
d) reacting a compound of formula



V

with an acylating agent of formula Y-CO-(C_1-C_6)-alkyl or Y'-SO_2-(C_1-C_6)-alkyl, wherein Y and Y' are representing suitably activating groups, e.g. halogens,

to obtain a compound of formula



Id

20. A compound of formula I according to any one of claims 1 to 18, when manufactured by a process according to claim 19.

21. A medicament containing one or more compounds as claimed in any one of claims 1 to 18 and pharmaceutically acceptable excipients for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

22. The medicament according to claim 21 for the treatment and prevention of Alzheimer's disease and senile dementia.

23. A compound of formula I according to any one of claims 1 to 18 as well as its pharmaceutically acceptable salts for the treatment or prevention of diseases.

24. The use of a compound of formula I according to any one of claims 1 to 18 as well as its pharmaceutically acceptable salts for the manufacture of medicaments for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

25. The use according to claim 24, wherein the disease is Alzheimer's disease or senile dementia.

26. The invention as herein before described.

***